L5 ANSWER 1 OF 11 CANCERLIT
ACCESSION NUMBER: 1998701809 CANCERLIT
DOCUMENT NUMBER: 98701809
TITLE: ALPHA-1-ACID GLYCOPROTEIN IS AN INDEPENDENT PREDICTOR OF EFFICACY AND SURVIVAL IN NSCLC PATIENTS TREATED WITH **DOCETAXEL** (**TAXOTERE**[trade]) (Meeting abstract).
AUTHOR: Bruno R; Olivares R; Berille J; Lebras E; Hammershaimb L; Rigas J R
CORPORATE SOURCE: Rhone-Poulenc Rorer Drug Metabolism and Pharmacokinetics, Biostatistics and Oncology, Antony, France and Collegeville, PA Dartmouth Hitchcock Medical Center, Lebanon, NH.
SOURCE: Proc Annu Meet Am Soc Clin Oncol, **(1998)** 17 A1812.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 20000616
Last Updated on STN: 20000616

AB Baseline alpha-1-acid glycoprotein (**AAG**) and **docetaxel** (D) clearance (and/or exposure) were previously found to be independent predictors of D safety (all tumor types combined) and of time to progression (TTP) in NSCLC (1). The predictors of treatment outcome and survival of advanced NSCLC patients entered in 4 Phase II studies (n = 180) of D (100 mg/m[Superscript 2]) were investigated using logistic and Cox multivariate regressions. Univariate analysis showed that compared to patients with high **AAG** (>=1.92 g/L (75 percentile)), patients with low **AAG** (<=1.09 g/L (25 percentile)) experienced more side effects (e.g. febrile neutropenia: 19% vs. 2.3%, p = 0.02) but had a higher response rate (44% vs. 14%, p = 0.002), a longer TTP (18 vs. 9.7 weeks, p = 0.006) and a much longer survival: 16 months compared to 5.2 months (p < 0.0001). In multivariate models, in addition to TTP (1), **AAG** was an independent prognostic factor for the incidence of severe side effects at first cycle (p = 0.006 with an interaction with D clearance), for response rate (odds ratio for non response in high **AAG** patients: 5.5, p = 0.006), and for survival (p < 0.0001). In conclusion, low **AAG** is independently associated with better efficacy and longer survival in advanced NSCLC treated with **docetaxel**. (1) R. Bruno et al. Population pharmacokinetics/pharmacodynamics of **docetaxel** in phase II studies in patients with cancer. J. Clin. Oncol., in press.
(C) American Society of Clinical Oncology 1998.

L5 ANSWER 2 OF 11 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998077107 EMBASE
TITLE: Conduct of phase I trials in children with cancer.
AUTHOR: Smith M.; Bernstein M.; Bleyer W.A.; Borsi J.D.; Ho P.; Lewis I.J.; Pearson A.; Pein F.; Pratt C.; Reaman G.; Riccardi R.; Seibel N.; Trueworthy R.; Ungerleider R.; Vassal G.; Vietti T.
CORPORATE SOURCE: Dr. M. Smith, Pediatric Section, Clinical Investigations Branch, CTEP, Executive Plaza North, Bethesda, MD 20892, United States. smithm@ctep.nci.nih.gov
SOURCE: Journal of Clinical Oncology, (1998) 16/3 (966-978).
Refs: 142
ISSN: 0732-183X CODEN: JCONDN
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
016 Cancer
037 Drug Literature Index
LANGUAGE: English

SUMMARY LANGUAGE: English

AB Purpose and Methods: Future progress in the care of children with cancer requires appropriate evaluations of promising new agents for pediatric indications, beginning with well-conducted phase I trials. This report summarizes current guidelines for the conduct of pediatric phase I trials and represents a consensus between American and European investigators. The primary objective of pediatric phase I trials is to define safe and appropriate doses and schedules of new agents that can subsequently be used in phase II trials to test for activity against specific childhood malignancies. Prioritization of agents for evaluation in children is critical, since many more investigational agents are evaluated in adult patients than can be systematically evaluated in children. Considerations used in prioritizing agents include activity in xenograft models, novel mechanism of action, favorable drug-resistance profile, and activity observed in adult trials of the agent. Results and Conclusion: Distinctive characteristics of pediatric phase I trials, in comparison to adult phase I trials, include the necessity for multiinstitutional participation and their higher starting dose (typically 80% of the adult maximum-tolerated dose [MTD]), both of which reflect the relative unavailability of appropriate patients. The application of uniform eligibility criteria and standard definitions for MTD and dose-limiting toxicity (DLT) help to assure that pediatric phase I trials are safely conducted and reliably identify appropriate doses and schedules of agents for phase II evaluation. Where possible, pediatric phase I trials also define the pharmacokinetic behavior of new agents in children.

L5 ANSWER 3 OF 11 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 1998:914576 SCISEARCH
THE GENUINE ARTICLE: 137ZN
TITLE: Serum alpha-1-acid glycoprotein (**AAG**) is an independent prognostic factor for efficacy and survival in patients with inoperable non small cell lung cancer (NSCLC) treated with **Taxotere**(R)
AUTHOR: LeChevalier T (Reprint); Berille J; Olivares R; Bruno R; Hammershaimb L; Bizzari J P
CORPORATE SOURCE: RHONE POULENC RORER, ANTONY, FRANCE; INST GUSTAVE ROUSSY, VILLEJUIF, FRANCE; RHONE POULENC RORER, COLLEGEVILLE, PA
COUNTRY OF AUTHOR: FRANCE; USA
SOURCE: ANNALS OF ONCOLOGY, (**NOV 1998**) Vol. 9, Supp. [4], pp. P414-P414.
Publisher: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA DORDRECHT, NETHERLANDS.
ISSN: 0923-7534.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L5 ANSWER 4 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:257450 BIOSIS
DOCUMENT NUMBER: PREV199800257450
TITLE: Prothymosin **alpha1** enhances the interleukin-2 activated killer cell adhesion to and immunotoxicity against **docetaxel**-treated HT-29 colon carcinoma cells in vitro.
AUTHOR(S): Gruenberg, Elke; Eckert, Klaus; Maurer, H. Rainer (1)
CORPORATE SOURCE: (1) Inst. Pharm., Freien Univ. Berlin, Dep. Pharm. Biochem., Kelchstr. 31, D-12169 Berlin Germany
SOURCE: International Journal of Thymology, (**Nov., 1997**) Vol. 5, No. 8-9, pp. 415-423.
ISSN: 0943-1675.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English; German

AB Natural killer (NK) and interleukin-2 (IL-2) activated killer (LAK) cell mediated lysis of tumor cells may vary, e.g., depending on the stage of tumor cell differentiation. In case of the colorectal tumor cell line HT-29, **docetaxel**, besides being an antiproliferative agent, induces HT-29 cell differentiation. Using this inducer we studied the effect of the thymic polypeptide prothymosin **alpha1** (Proalpha1) on the LAK-cell-activity against untreated and differentiated HT-29 cells, as measured by lymphocyte adhesion, immunocytotoxicity and secretion of cytokines. It was observed that unstimulated lymphocytes showed a better adherence to and higher cytotoxicity against **docetaxel** (3X10-9 M) treated cells. Generation of LAK-cells by IL-2 (10 U/ml) increased lymphocyte adhesion as well as tumor cell lysis more effectively on treated cells. While anti-LFA-3, -CD44v6, - CD15, -VLA-4 and CD13 mAb reduced lymphocyte adhesion, CEA mAb increased the binding to the tumor cells. The stronger adherence of the LAK-cells to treated HT-29 cells appears to be mediated by the VLA-4 adhesion molecule. Proalpha1 stimulates adhesion to and immunocytotoxicity of LAK-cells against tumor cells. With respect to these parameters, combination with low (10 U/ml) IL-2 was equally effective compared with high (20 U/ml) doses of IL-2. Treated HT-29 cells were more susceptible to Proalpha1-stimulated LAK-cells. Increased cell adhesion and immunocytotoxicity of LAK-cells was associated with increased secretion of TNF-alpha, with no significant participation of IFNgamma. Thus, Proalpha1 in combination with IL-2 is more effective in lymphocyte mediated tumor cell lysis of **docetaxel**-treated, differentiated HT-29 colon carcinoma cells. This may provide a rational basis for the improvement of selected chemoimmuno-therapy protocols.

L5 ANSWER 5 OF 11 CANCERLIT
ACCESSION NUMBER: 97605415 CANCERLIT
DOCUMENT NUMBER: 97605415
TITLE: Population pharmacokinetics of **docetaxel** in Japanese patients (Meeting abstract).
AUTHOR: Tanigawara Y; Sasaki Y; Otsu T; Fujii H; Kashimura M; Sasaki T; Okumura K; Taguchi T
CORPORATE SOURCE: Dept. of Pharmacy, Kobe University Hospital, Kobe 650, Japan.
SOURCE: Proc Annu Meet Am Soc Clin Oncol, **(1996)** 15 A1518.
ISSN: 0732-183X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19980417
Last Updated on STN: 19980417

AB Pharmacokinetics of **docetaxel** (**Taxotere**) have been investigated by a population analysis using the 662 plasma concentration data obtained from 102 Japanese patients who participated in phase I and II clinical trials. **Docetaxel** disposition was described by a 3-compartment linear model at the dose range of 10-90 mg/m2. NONMEM analysis showed that the **docetaxel** clearance was related to the body surface area (BSA, m2) and serum albumin level (ALB, g/100 ml) and inversely correlated with alpha 1-acid glycoprotein level (**AAG**, mg/100 ml) and age. The patients having hepatic dysfunction (HEP1=1) indicated by the elevation of GOT or GPT greater than 60 IU/I showed 12% reduction in clearance. The population mean of clearance was described by CL=BSA (37.0-0.0629AAG-0.192AGE+0.542ALB) (1-0.124HEP1). The remaining interindividual variability was 26%. These results were comparable to those obtained in European and American population (Bruno et al, ASCO; 1995), and the mean clearance for the Japanese and European/American were 20.3 and 20.6 (L/hr/m2), respectively. This finding suggests no racial difference in the elimination of **docetaxel**. Since dose-limiting toxicity (myelosuppression) was related to the AUC according to a

pharmacodynamic analysis, the present population model is useful for optimizing an individual dose of **docetaxel** to reach the target AUC level.
(C) American Society of Clinical Oncology 1997.

L5 ANSWER 6 OF 11 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 97029333 MEDLINE
DOCUMENT NUMBER: 97029333 PubMed ID: 8875345
TITLE: A population pharmacokinetic model for **docetaxel** (**Taxotere**): model building and validation.
AUTHOR: Bruno R; Vivier N; Vergniol J C; De Phillips S L; Montay G; Sheiner L B
CORPORATE SOURCE: Department of Laboratory Medicine, School of Medicine, University of California, San Francisco, USA.
SOURCE: JOURNAL OF PHARMACOKINETICS AND BIOPHARMACEUTICS, **(1996 Apr)** 24 (2) 153-72.
Journal code: 0357115. ISSN: 0090-466X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970115

AB A sparse sampling strategy (3 samples per patient, 521 patients) was implemented in 22 Phase 2 studies of **docetaxel** (**Taxotere**) at the first treatment cycle for a prospective population pharmacokinetic evaluation. In addition to the 521 Phase 2 patients, 26 (data rich) patients from Phase I studies were included in the analysis. NONMEM analysis of an index set of 280 patients demonstrated that **docetaxel** clearance (CL) is related to alpha 1-acid glycoprotein (**AAG**) level, hepatic function (HEP), age (AGE), and body surface area (BSA). The index set population model prediction of CL was compared to that of a naive predictor (NP) using a validation set of 267 patients. Qualitatively, the dependence of CL on **AAG**, AGE, BSA, and HEP seen in the index set population model was supported in the validation set. Quantitatively, for the validation set patients overall, the performance (bias, precision) of the model was good (7 and 21%, respectively), although not better than that of the NP. However, in all the subpopulations with decreased CL, the model performed better than the NP; the more the CL differed from the population average, the better the performance. For example, in the subpopulation of patients with **AAG** levels > 2.27 g/L (n = 26), bias and precision of model predictions were 24 and 32% vs. 53 and 53%, respectively, for the NP. The prediction of CL using the model was better (than that of the NP) in 73% of the patients. The population model was redetermined using the whole population of 547 patients and a new covariate, albumin plasma level, was found to be a significant predictor in addition to those found previously. In the final model, HEP, **AAG**, and BSA are the main predictors of **docetaxel** CL.

L5 ANSWER 7 OF 11 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97070909 MEDLINE
DOCUMENT NUMBER: 97070909 PubMed ID: 8913835
TITLE: **Docetaxel** serum protein binding with high affinity to alpha 1-acid glycoprotein.
AUTHOR: Urien S; Barre J; Morin C; Paccaly A; Montay G; Tillement J P
CORPORATE SOURCE: Laboratoire de Pharmacologie, Faculte de Medecine, Creteil, France.

SOURCE: INVESTIGATIONAL NEW DRUGS, **(1996)** 14 (2) 147-51.
Journal code: 8309330. ISSN: 0167-6997.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970306
Last Updated on STN: 19970306
Entered Medline: 19970224

AB The binding of **docetaxel** to human plasma proteins was studied by ultrafiltration at 37 degrees C and pH 7.4. **Docetaxel** was extensively (> 98%) plasma protein bound. At clinically relevant concentrations (1-5 micrograms/ml), the plasma binding was concentration-independent. Lipoproteins, **alpha1**-acid glycoprotein and albumin were the main carriers of **docetaxel** in plasma, and owing to the high interindividual variability of **alpha1**-acid glycoprotein plasma concentration, particularly in cancer, it was concluded that **alpha1**-acid glycoprotein should be the main determinant of **docetaxel** plasma binding variability. Drugs potentially coadministered with **docetaxel** (cisplatin, dexamethasone, doxorubicin, etoposide, vinblastine) did not modify the plasma binding of **docetaxel**. In blood, **docetaxel** was found to be mainly located in the plasma compartment (less than 15% associated to erythrocytes).

L5 ANSWER 8 OF 11 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 95254452 MEDLINE
DOCUMENT NUMBER: 95254452 PubMed ID: 7736407
TITLE: Modulation of P-glycoprotein activity by estramustine is limited by binding to plasma proteins.
AUTHOR: Smith C D; Zilfou J T; Zhang X; Hudes G R; Tew K D
CORPORATE SOURCE: Department of Pharmacology, Fox Chase Cancer Center, Philadelphia, PA 19111, USA.
SOURCE: CANCER, **(1995 May 15)** 75 (10) 2597-604.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950615
Last Updated on STN: 19970203
Entered Medline: 19950608

AB BACKGROUND. Estramustine previously has been shown to interact with P-glycoprotein and to restore intracellular accumulation of vinblastine and **paclitaxel** in cells overexpressing this drug transporter. However, the ability of estramustine to potentiate the cytotoxicities of several drugs was less than that expected. To resolve this apparent discordance, the authors examined the effects of serum on the actions of estramustine. METHODS. The cytotoxicities of anticancer drugs with or without estramustine or verapamil toward MCF-7 breast carcinoma cells and a P-glycoprotein-overexpressing subline MCF-7/ADR were determined using the sulforhodamine-binding assay. The extent of intracellular accumulation of [3H]vinblastine and [3H]**paclitaxel** was determined for each using standard methods, and the binding of radiolabeled drugs to plasma proteins was characterized by equilibrium dialysis. RESULTS. Without serum, the sensitivities of MCF-7/ADR cells to several P-glycoprotein-transported drugs were increased by estramustine and verapamil. Conversely, when the cells were treated with a 10% serum, the cytotoxicities of these drugs were increased by verapamil, but not by estramustine. Without serum, intracellular accumulation of [3H]vinblastine and [3H]**paclitaxel** by MCF-7/ADR cells was increased markedly by verapamil and estramustine; however, serum suppressed the effects of

estramustine much more strongly than those of verapamil. Equilibrium dialysis experiments demonstrated that [3H]estramustine binds to plasma proteins, predominantly albumin, whereas [3H]**paclitaxel** binds to albumin and alpha 1-acid-glycoprotein, and [3H]vinblastine binds predominantly to alpha 1-acid-glycoprotein. CONCLUSION. Although estramustine can bind to P-glycoprotein, its effectiveness as a reversing agent in vivo likely is limited by binding to plasma proteins.

L5 ANSWER 9 OF 11 CANCERLIT
ACCESSION NUMBER: 96603238 CANCERLIT
DOCUMENT NUMBER: 96603238
TITLE: Population pharmacokinetics/pharmacodynamics (PK/PD) of **docetaxel** (**Taxotere**) in phase II studies (Meeting abstract).
AUTHOR: Bruno R; Hille D; Thomas L; Riva A; Sheiner L B
CORPORATE SOURCE: Rhone-Poulenc Rorer, Antony, France.
SOURCE: Proc Annu Meet Am Soc Clin Oncol, **(1995)** 14 A1471.
ISSN: 0732-183X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199604
ENTRY DATE: Entered STN: 19970509
Last Updated on STN: 19970509

AB A sparse sampling strategy (3 samples per patient; pt) was implemented in 22 phase II studies (577 pts) of **docetaxel** (D) for prospective population PK/PD evaluation. Population PK analysis (547 pts, nonlinear mixed effect modelling) demonstrated that interpatient variability (50.2%) of D clearance (CL; mean: 36.7 l/hr) correlates with body surface area (BSA), alpha 1-acid glycoprotein (**AAG**) plasma level and hepatic enzyme plasma levels. PK/PD analysis (logistic and Cox regression models) using Bayesian estimates of individual pt CL demonstrated that, after adjustment for the effects of other covariates, CL variability is a strong predictor of the odds of grade 4 neutropenia (500 pts, Grade 4: 62%), and is weakly related to the risk of fluid retention (569 pts, occurrence 50%). CL variability related to BSA is adequately accounted for by dosing D in mg/m2. As **AAG** is by itself a predictor of PD effects, it was not possible to assess whether **AAG** influences PD through its effect on PK. Finally, no evidence was found of an increased odds of neutropenia grade 4 in the subpopulation of pts with elevated hepatic enzymes (16 pts, grade 4: 63%) despite a 30% reduction in CL, nor do the data support a relationship between CL and response rate (RR) in breast cancer (146 pts, RR: 59%) and NSC lung cancer (151 pts, RR: 29%).
(C) American Society of Clinical Oncology 1997.

L5 ANSWER 10 OF 11 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 93355098 MEDLINE
DOCUMENT NUMBER: 93355098 PubMed ID: 8102493
TITLE: Binding of taxol to human plasma, albumin and alpha 1-acid glycoprotein.
AUTHOR: Kumar G N; Walle U K; Bhalla K N; Walle T
CORPORATE SOURCE: Department of Cell and Molecular Pharmacology and Experimental Therapeutics, Medical University of South Carolina, Charleston 29425.
SOURCE: RESEARCH COMMUNICATIONS IN CHEMICAL PATHOLOGY AND PHARMACOLOGY, **(1993 Jun)** 80 (3) 337-44.
Journal code: 0244734. ISSN: 0034-5164.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199309
ENTRY DATE: Entered STN: 19931001

Last Updated on STN: 19950206
Entered Medline: 19930915

AB The binding of taxol to human plasma and to individual plasma proteins was studied by equilibrium dialysis. Taxol was found to bind extensively (about 95%) without a significant difference between healthy volunteers and cancer patients. At clinically relevant concentrations (0.1-6 microM), the binding was found to be concentration independent, indicating nonspecific hydrophobic binding. Human serum albumin and alpha 1-acid glycoprotein were found to contribute about equally to the binding, with a minor contribution from lipoproteins. None of the drugs commonly coadministered with taxol (dexamethasone, diphenhydramine, ranitidine, doxorubicin, 5-fluorouracil and cisplatin) altered the binding of taxol significantly. The protein binding of taxol was found to dramatically decrease the red blood cell uptake of taxol.

L5 ANSWER 11 OF 11 MEDLINE
ACCESSION NUMBER: 92357764 MEDLINE
DOCUMENT NUMBER: 92357764 PubMed ID: 1353884
TITLE: A role for microtubules in sorting endocytic vesicles in rat hepatocytes.
AUTHOR: Goltz J S; Wolkoff A W; Novikoff P M; Stockert R J; Satir P
CORPORATE SOURCE: Department of Anatomy and Structural Biology, Albert Einstein College of Medicine, Bronx, NY 10461.
CONTRACT NUMBER: DK-41918 (NIDDK)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1992 Aug 1)** 89 (15) 7026-30.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 19920925
Last Updated on STN: 19950206
Entered Medline: 19920904

AB The vectorial nature of hepatocyte receptor-mediated endocytosis (RME) and its susceptibility to cytoskeletal disruptors has suggested that a polarized network of microtubules plays a vital role in directed movement during sorting. Using as markers a well-known ligand, asialoorosomucoid, and its receptor, we have isolated endocytic vesicles that bind directly to and interact with stabilized endogenous hepatocyte microtubules at specific times during a synchronous, experimentally initiated, single wave of RME. Both ligand- and receptor-containing vesicles copelleted with microtubules in the absence of ATP but did not pellet under similar conditions when microtubules were not polymerized. When 5 mM ATP was added to preparations of microtubule-bound vesicles, ligand-containing vesicles were released into the supernatant, while receptor-containing vesicles remained immobilized on the microtubules. Release of ligand-containing vesicles from microtubules was prevented by monensin treatment during the endocytic wave. Several proteins, including the microtubule motor protein cytoplasmic dynein, were present in these preparations and were released from microtubule pellets by ATP addition concomitantly with ligand. These results suggest that receptor domains within the endosome can be immobilized by attachment to microtubules so that, following monensin-sensitive dissociation of ligand from receptor, ligand-containing vesicles can be pulled along microtubules away from the receptor domains by a motor molecule, such as cytoplasmic dynein, thereby delineating sorting.

=> d his

(FILE 'HOME' ENTERED AT 12:20:58 ON 28 JAN 2003)

```
     FILE 'MEDLINE, CANCERLIT, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 12:21:06
     ON 28 JAN 2003
L1         39687 S (TAXOID OR ?TAXEL OR TAXOTERE)
L2         44114 S (OROSOMUCOID OR AGP OR AAG OR ALPHA1?)
L3            53 S L1 AND L2
L4            20 S L3 AND PY<=1998
L5            11 DUP REM L4 (9 DUPLICATES REMOVED)

=> s (orosomucoid OR AGP OR AAG OR alpha-1-acid)
   4 FILES SEARCHED...
L6         19061 (OROSOMUCOID OR AGP OR AAG OR ALPHA-1-ACID)

=> s taxoid or taxol or ?taxel or taxotere
L7         54407 TAXOID OR TAXOL OR ?TAXEL OR TAXOTERE

=> s l6 and l7
L8            70 L6 AND L7

=> s l8 and py<=1998
   2 FILES SEARCHED...
   3 FILES SEARCHED...
L9            27 L8 AND PY<=1998

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10           11 DUP REM L9 (16 DUPLICATES REMOVED)

=> d ibib abs 1-11

L10  ANSWER 1 OF 11     CANCERLIT
ACCESSION NUMBER:    1998701809     CANCERLIT
DOCUMENT NUMBER:     98701809
TITLE:               ALPHA-1-ACID GLYCOPROTEIN IS
                     AN INDEPENDENT PREDICTOR OF EFFICACY AND SURVIVAL IN NSCLC
                     PATIENTS TREATED WITH DOCETAXEL (TAXOTERE
                     [trade]) (Meeting abstract).
AUTHOR:              Bruno R; Olivares R; Berille J; Lebras E; Hammershaimb L;
                     Rigas J R
CORPORATE SOURCE:    Rhone-Poulenc Rorer Drug Metabolism and Pharmacokinetics,
                     Biostatistics and Oncology, Antony, France and
                     Collegeville, PA Dartmouth Hitchcock Medical Center,
                     Lebanon, NH.
SOURCE:              Proc Annu Meet Am Soc Clin Oncol, (1998) 17
                     A1812.
DOCUMENT TYPE:       (MEETING ABSTRACTS)
LANGUAGE:            English
FILE SEGMENT:        Institute for Cell and Developmental Biology
ENTRY MONTH:         199910
ENTRY DATE:          Entered STN: 20000616
                     Last Updated on STN: 20000616
AB   Baseline alpha-1-acid glycoprotein (
     AAG) and docetaxel (D) clearance (and/or exposure) were
     previously found to be independent predictors of D safety (all tumor types
     combined) and of time to progression (TTP) in NSCLC (1). The predictors of
     treatment outcome and survival of advanced NSCLC patients entered in 4
     Phase II studies (n = 180) of D (100 mg/m[Superscript 2]) were
     investigated using logistic and Cox multivariate regressions. Univariate
     analysis showed that compared to patients with high AAG (>=1.92
     g/L (75 percentile)), patients with low AAG (<=1.09 g/L (25
     percentile)) experienced more side effects (e.g. febrile neutropenia: 19%
     vs. 2.3%, p = 0.02) but had a higher response rate (44% vs. 14%, p =
     0.002), a longer TTP (18 vs. 9.7 weeks, p = 0.006) and a much longer
     survival: 16 months compared to 5.2 months (p < 0.0001). In multivariate
```

models, in addition to TTP (1), **AAG** was an independent prognostic factor for the incidence of severe side effects at first cycle ($p = 0.006$ with an interaction with D clearance), for response rate (odds ratio for non response in high **AAG** patients: 5.5, $p = 0.006$), and for survival ($p < 0.0001$). In conclusion, low **AAG** is independently associated with better efficacy and longer survival in advanced NSCLC treated with **docetaxel**. (1) R. Bruno et al. Population pharmacokinetics/pharmacodynamics of **docetaxel** in phase II studies in patients with cancer. J. Clin. Oncol., in press.
(C) American Society of Clinical Oncology 1998.

L10 ANSWER 2 OF 11 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 1998:914576 SCISEARCH
THE GENUINE ARTICLE: 137ZN
TITLE: Serum **alpha-1-acid** glycoprotein (**AAG**) is an independent prognostic factor for efficacy and survival in patients with inoperable non small cell lung cancer (NSCLC) treated with **Taxotere**(R)
AUTHOR: LeChevalier T (Reprint); Berille J; Olivares R; Bruno R; Hammershaimb L; Bizzari J P
CORPORATE SOURCE: RHONE POULENC RORER, ANTONY, FRANCE; INST GUSTAVE ROUSSY, VILLEJUIF, FRANCE; RHONE POULENC RORER, COLLEGEVILLE, PA
COUNTRY OF AUTHOR: FRANCE; USA
SOURCE: ANNALS OF ONCOLOGY, (**NOV 1998**) Vol. 9, Supp. [4], pp. P414-P414.
Publisher: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA DORDRECHT, NETHERLANDS.
ISSN: 0923-7534.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L10 ANSWER 3 OF 11 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 1998:66730 SCISEARCH
THE GENUINE ARTICLE: YQ270
TITLE: Population pharmacokinetics/pharmacodynamics of **docetaxel** in phase II studies in patients with cancer
AUTHOR: Bruno R (Reprint); Hille D; Riva A; Vivier N; Huinnink W W T B; vanOosterom A T; Kaye S B; Verweij J; Fossella F V; Valero V; Rigas J R; Seidman A D; Chevallier B; Fumoleau P; Burris H A; Ravclin P M; Sheiner L B
CORPORATE SOURCE: RHONE POULENC RORER, DEPT DRUG METAB & PHARMACOKINET, BOX 58, 20 AVE RAYMOND ARON, F-92165 ANTONY, FRANCE (Reprint); RHONE POULENC RORER, DEPT STAT, F-92165 ANTONY, FRANCE; RHONE POULENC RORER, DEPT ONCOL, F-92165 ANTONY, FRANCE; RHONE POULENC RORER, DEPT DRUG METAB & PHARMACOKINET, COLLEGEVILLE, PA; RHONE POULENC RORER, DEPT STAT, COLLEGEVILLE, PA; RHONE POULENC RORER, DEPT ONCOL, COLLEGEVILLE, PA; CANC REG LUTTE CONTRE CANC, NANTES, FRANCE; NETHERLANDS CANC INST, AMSTERDAM, NETHERLANDS; ROTTERDAM CANC INST, ROTTERDAM, NETHERLANDS; UNIV ZIEKENHUIS, EDEGEM, BELGIUM; UNIV GLASGOW, WESTERN INFIRM, GLASGOW G11 6NT, LANARK, SCOTLAND; UNIV TEXAS, MD ANDERSON CANCER CTR, HOUSTON, TX 77030; UNIV TEXAS, HLTH SCI CTR, SAN ANTONIO, TX; MEM SLOAN KETTERING CANC CTR, NEW YORK, NY 10021; UNIV CALIF SAN FRANCISCO, SAN FRANCISCO, CA 94143
COUNTRY OF AUTHOR: FRANCE; USA; NETHERLANDS; BELGIUM; SCOTLAND
SOURCE: JOURNAL OF CLINICAL ONCOLOGY, (**JAN 1998**) Vol. 16, No. 1, pp. 187-196.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST

CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0732-183X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 54

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Purpose: The population pkarmacokinetic/pharmacodynamic (PK/PD) approach was prospectively integrated in the clinical development of **docetaxel** to assess the PK profile in a large population of patients and investigate systemic exposure as a prognostic factor for clinical outcome,

Patients and Methods: PK analysis was performed at first course in 24 phase II studies of **docetaxel** monotherapy using four randomized limited-sampling schedules, Bayesian estimates of clearance (CL), area under the concentration-time curve (AUC), and peak and duration of plasma levels greater than threshold levels were used as measures of exposure. PD data included for efficacy, response rate, time to first response, and time to progression (TTP) in breast cancer and non-small-cell lung cancer (NSCLC), and for toxicity, grade 4 neutropenia, and febrile neutropenia at first course and time to onset of fluid retention, PK/PD analysis was conducted using logistic and Cox multivariate regression models,

Results: PK protocol implementation was successful. Most of the patients registered (721 of 936, 77%) were sampled and 68% were assessable for PK (640 patients), First-course **docetaxel** AUC was a significant predictor (P = .0232) of TTP in NSCLC (n = 151), **Docetaxel** CL was ct strong independent predictor (P < .0001) of both grade 4 neutropenia and febrile neutropenia (n = 582). Cumulative dose was the strongest predictor (P < .0001) of the time to onset of fluid retention (n = 631). However,the duration of exposure over 0.20 mu mol/L (0.16 mu g/mL) at first course was an independent predictor (P = .0029). Few patients (n = 25, 4%) received the recommended dexamethasone premedication.

Conclusion: First-course **docetaxel** PK is a predictor of first-course hematologic toxicity, but also of fluid retention, which is cumulative in nature. Patients with elevated hepatic enzymes have a 27% reduction in **docetaxel** CL and are at a higher risk of toxicity, A starting dose of 75 mg/m(2) is currently being evaluated in this population. prospective implementation of large-scale population PK/PD evaluation is feasible in early drug development and this approach generates clinically relevant findings, (C) 1998 by American Society of Clinical Oncology.

L10 ANSWER 4 OF 11 CANCERLIT
ACCESSION NUMBER: 97605415 CANCERLIT
DOCUMENT NUMBER: 97605415
TITLE: Population pharmacokinetics of **docetaxel** in Japanese patients (Meeting abstract).
AUTHOR: Tanigawara Y; Sasaki Y; Otsu T; Fujii H; Kashimura M; Sasaki T; Okumura K; Taguchi T
CORPORATE SOURCE: Dept. of Pharmacy, Kobe University Hospital, Kobe 650, Japan.
SOURCE: Proc Annu Meet Am Soc Clin Oncol, **(1996)** 15 A1518.
ISSN: 0732-183X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19980417
Last Updated on STN: 19980417

AB Pharmacokinetics of **docetaxel** (**Taxotere**) have been investigated by a population analysis using the 662 plasma concentration data obtained from 102 Japanese patients who participated in phase I and

II clinical trials. **Docetaxel** disposition was described by a 3-compartment linear model at the dose range of 10-90 mg/m2. NONMEM analysis showed that the **docetaxel** clearance was related to the body surface area (BSA, m2) and serum albumin level (ALB, g/100 ml) and inversely correlated with **alpha 1-acid** glycoprotein level (**AAG**, mg/100 ml) and age. The patients having hepatic dysfunction (HEP1=1) indicated by the elevation of GOT or GPT greater than 60 IU/I showed 12% reduction in clearance. The population mean of clearance was described by CL=BSA (37.0-0.0629AAG-0.192AGE+0.542ALB) (1-0.124HEP1). The remaining interindividual variability was 26%. These results were comparable to those obtained in European and American population (Bruno et al, ASCO; 1995), and the mean clearance for the Japanese and European/American were 20.3 and 20.6 (L/hr/m2), respectively. This finding suggests no racial difference in the elimination of **docetaxel**. Since dose-limiting toxicity (myelosuppression) was related to the AUC according to a pharmacodynamic analysis, the present population model is useful for optimizing an individual dose of **docetaxel** to reach the target AUC level.
(C) American Society of Clinical Oncology 1997.

L10 ANSWER 5 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:8037 BIOSIS
DOCUMENT NUMBER: PREV199799307240
TITLE: In vitro evaluation of the protein binding of GW918, a potent inhibitor of P-glycoprotein.
AUTHOR(S): Mann, M. B. (1); Mosley, A. (1); Nystrom, D. D.; Brouwer, K. R.; Brouwer, K. L. R. (1)
CORPORATE SOURCE: (1) Div. Pharmaceutics, Sch. Pharmacy, Univ. North Carolina, Chapel Hill, NC 27599 USA
SOURCE: Pharmaceutical Research (New York), (1996) Vol. 13, No. 9 SUPPL., pp. S420.
Meeting Info.: Annual Meeting of the American Association of Pharmaceutical Scientists Seattle, Washington, USA October 27-31, 1996
ISSN: 0724-8741.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L10 ANSWER 6 OF 11 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 97029333 MEDLINE
DOCUMENT NUMBER: 97029333 PubMed ID: 8875345
TITLE: A population pharmacokinetic model for **docetaxel** (**Taxotere**): model building and validation.
AUTHOR: Bruno R; Vivler N; Vergniol J C; De Phillips S L; Montay G; Sheiner L B
CORPORATE SOURCE: Department of Laboratory Medicine, School of Medicine, University of California, San Francisco, USA.
SOURCE: JOURNAL OF PHARMACOKINETICS AND BIOPHARMACEUTICS, **(1996 Apr)** 24 (2) 153-72.
Journal code: 0357115. ISSN: 0090-466X.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970115
AB A sparse sampling strategy (3 samples per patient, 521 patients) was implemented in 22 Phase 2 studies of **docetaxel** (**Taxotere**) at the first treatment cycle for a prospective population

pharmacokinetic evaluation. In addition to the 521 Phase 2 patients, 26 (data rich) patients from Phase I studies were included in the analysis. NONMEM analysis of an index set of 280 patients demonstrated that **docetaxel** clearance (CL) is related to **alpha 1 -acid** glycoprotein (**AAG**) level, hepatic function (HEP), age (AGE), and body surface area (BSA). The index set population model prediction of CL was compared to that of a naive predictor (NP) using a validation set of 267 patients. Qualitatively, the dependence of CL on **AAG**, AGE, BSA, and HEP seen in the index set population model was supported in the validation set. Quantitatively, for the validation set patients overall, the performance (bias, precision) of the model was good (7 and 21%, respectively), although not better than that of the NP. However, in all the subpopulations with decreased CL, the model performed better than the NP; the more the CL differed from the population average, the better the performance. For example, in the subpopulation of patients with **AAG** levels > 2.27 g/L (n = 26), bias and precision of model predictions were 24 and 32% vs. 53 and 53%, respectively, for the NP. The prediction of CL using the model was better (than that of the NP) in 73% of the patients. The population model was redetermined using the whole population of 547 patients and a new covariate, albumin plasma level, was found to be a significant predictor in addition to those found previously. In the final model, HEP, **AAG**, and BSA are the main predictors of **docetaxel** CL.

L10 ANSWER 7 OF 11 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97070909 MEDLINE
DOCUMENT NUMBER: 97070909 PubMed ID: 8913835
TITLE: **Docetaxel** serum protein binding with high affinity to **alpha 1-acid** glycoprotein.
AUTHOR: Urien S; Barre J; Morin C; Paccaly A; Montay G; Tillement J P
CORPORATE SOURCE: Laboratoire de Pharmacologie, Faculte de Medecine, Creteil, France.
SOURCE: INVESTIGATIONAL NEW DRUGS, **(1996)** 14 (2) 147-51. Journal code: 8309330. ISSN: 0167-6997.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970306
Last Updated on STN: 19970306
Entered Medline: 19970224

AB The binding of **docetaxel** to human plasma proteins was studied by ultrafiltration at 37 degrees C and pH 7.4. **Docetaxel** was extensively (> 98%) plasma protein bound. At clinically relevant concentrations (1-5 micrograms/ml), the plasma binding was concentration-independent. Lipoproteins, alpha1-acid glycoprotein and albumin were the main carriers of **docetaxel** in plasma, and owing to the high interindividual variability of alpha1-acid glycoprotein plasma concentration, particularly in cancer, it was concluded that alpha1-acid glycoprotein should be the main determinant of **docetaxel** plasma binding variability. Drugs potentially coadministered with **docetaxel** (cisplatin, dexamethasone, doxorubicin, etoposide, vinblastine) did not modify the plasma binding of **docetaxel**. In blood, **docetaxel** was found to be mainly located in the plasma compartment (less than 15% associated to erythrocytes).

L10 ANSWER 8 OF 11 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 95254452 MEDLINE
DOCUMENT NUMBER: 95254452 PubMed ID: 7736407
TITLE: Modulation of P-glycoprotein activity by estramustine is limited by binding to plasma proteins.

AUTHOR: Smith C D; Zilfou J T; Zhang X; Hudes G R; Tew K D
CORPORATE SOURCE: Department of Pharmacology, Fox Chase Cancer Center, Philadelphia, PA 19111, USA.
SOURCE: CANCER, **(1995 May 15)** 75 (10) 2597-604.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950615
Last Updated on STN: 19970203
Entered Medline: 19950608

AB BACKGROUND. Estramustine previously has been shown to interact with P-glycoprotein and to restore intracellular accumulation of vinblastine and **paclitaxel** in cells overexpressing this drug transporter. However, the ability of estramustine to potentiate the cytotoxicities of several drugs was less than that expected. To resolve this apparent discordance, the authors examined the effects of serum on the actions of estramustine. METHODS. The cytotoxicities of anticancer drugs with or without estramustine or verapamil toward MCF-7 breast carcinoma cells and a P-glycoprotein-overexpressing subline MCF-7/ADR were determined using the sulforhodamine-binding assay. The extent of intracellular accumulation of [3H]vinblastine and [3H]**paclitaxel** was determined for each using standard methods, and the binding of radiolabeled drugs to plasma proteins was characterized by equilibrium dialysis. RESULTS. Without serum, the sensitivities of MCF-7/ADR cells to several P-glycoprotein-transported drugs were increased by estramustine and verapamil. Conversely, when the cells were treated with a 10% serum, the cytotoxicities of these drugs were increased by verapamil, but not by estramustine. Without serum, intracellular accumulation of [3H]vinblastine and [3H]**paclitaxel** by MCF-7/ADR cells was increased markedly by verapamil and estramustine; however, serum suppressed the effects of estramustine much more strongly than those of verapamil. Equilibrium dialysis experiments demonstrated that [3H]estramustine binds to plasma proteins, predominantly albumin, whereas [3H]**paclitaxel** binds to albumin and **alpha 1-acid**-glycoprotein, and [3H]vinblastine binds predominantly to **alpha 1-acid**-glycoprotein. CONCLUSION. Although estramustine can bind to P-glycoprotein, its effectiveness as a reversing agent in vivo likely is limited by binding to plasma proteins.

L10 ANSWER 9 OF 11 CANCERLIT
ACCESSION NUMBER: 96603238 CANCERLIT
DOCUMENT NUMBER: 96603238
TITLE: Population pharmacokinetics/pharmacodynamics (PK/PD) of **docetaxel** (**Taxotere**) in phase II studies (Meeting abstract).
AUTHOR: Bruno R; Hille D; Thomas L; Riva A; Sheiner L B
CORPORATE SOURCE: Rhone-Poulenc Rorer, Antony, France.
SOURCE: Proc Annu Meet Am Soc Clin Oncol, **(1995)** 14 A1471.
ISSN: 0732-183X.
DOCUMENT TYPE: (MEETING ABSTRACTS)
LANGUAGE: English
FILE SEGMENT: Institute for Cell and Developmental Biology
ENTRY MONTH: 199604
ENTRY DATE: Entered STN: 19970509
Last Updated on STN: 19970509

AB A sparse sampling strategy (3 samples per patient; pt) was implemented in 22 phase II studies (577 pts) of **docetaxel** (D) for prospective population PK/PD evaluation. Population PK analysis (547 pts, nonlinear mixed effect modelling) demonstrated that interpatient variability (50.2%) of D clearance (CL; mean: 36.7 l/hr) correlates with body surface area

(BSA), **alpha 1-acid** glycoprotein (**AAG**) plasma level and hepatic enzyme plasma levels. PK/PD analysis (logistic and Cox regression models) using Bayesian estimates of individual pt CL demonstrated that, after adjustment for the effects of other covariates, CL variability is a strong predictor of the odds of grade 4 neutropenia (500 pts, Grade 4: 62%), and is weakly related to the risk of fluid retention (569 pts, occurrence 50%). CL variability related to BSA is adequately accounted for by dosing D in mg/m2. As **AAG** is by itself a predictor of PD effects, it was not possible to assess whether **AAG** influences PD through its effect on PK. Finally, no evidence was found of an increased odds of neutropenia grade 4 in the subpopulation of pts with elevated hepatic enzymes (16 pts, grade 4: 63%) despite a 30% reduction in CL, nor do the data support a relationship between CL and response rate (RR) in breast cancer (146 pts, RR: 59%) and NSC lung cancer (151 pts, RR: 29%).
(C) American Society of Clinical Oncology 1997.

L10 ANSWER 10 OF 11 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 93355098 MEDLINE
DOCUMENT NUMBER: 93355098 PubMed ID: 8102493
TITLE: Binding of **taxol** to human plasma, albumin and **alpha 1-acid** glycoprotein.
AUTHOR: Kumar G N; Walle U K; Bhalla K N; Walle T
CORPORATE SOURCE: Department of Cell and Molecular Pharmacology and Experimental Therapeutics, Medical University of South Carolina, Charleston 29425.
SOURCE: RESEARCH COMMUNICATIONS IN CHEMICAL PATHOLOGY AND PHARMACOLOGY, **(1993 Jun)** 80 (3) 337-44.
Journal code: 0244734. ISSN: 0034-5164.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199309
ENTRY DATE: Entered STN: 19931001
Last Updated on STN: 19950206
Entered Medline: 19930915

AB The binding of **taxol** to human plasma and to individual plasma proteins was studied by equilibrium dialysis. **Taxol** was found to bind extensively (about 95%) without a significant difference between healthy volunteers and cancer patients. At clinically relevant concentrations (0.1-6 microM), the binding was found to be concentration independent, indicating nonspecific hydrophobic binding. Human serum albumin and **alpha 1-acid** glycoprotein were found to contribute about equally to the binding, with a minor contribution from lipoproteins. None of the drugs commonly coadministered with **taxol** (dexamethasone, diphenhydramine, ranitidine, doxorubicin, 5-fluorouracil and cisplatin) altered the binding of **taxol** significantly. The protein binding of **taxol** was found to dramatically decrease the red blood cell uptake of **taxol** .

L10 ANSWER 11 OF 11 MEDLINE
ACCESSION NUMBER: 92357764 MEDLINE
DOCUMENT NUMBER: 92357764 PubMed ID: 1353884
TITLE: A role for microtubules in sorting endocytic vesicles in rat hepatocytes.
AUTHOR: Goltz J S; Wolkoff A W; Novikoff P M; Stockert R J; Satir P
CORPORATE SOURCE: Department of Anatomy and Structural Biology, Albert Einstein College of Medicine, Bronx, NY 10461.
CONTRACT NUMBER: DK-41918 (NIDDK)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1992 Aug 1)** 89 (15) 7026-30.

Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 19920925
Last Updated on STN: 19950206
Entered Medline: 19920904

AB The vectorial nature of hepatocyte receptor-mediated endocytosis (RME) and its susceptibility to cytoskeletal disruptors has suggested that a polarized network of microtubules plays a vital role in directed movement during sorting. Using as markers a well-known ligand, asialoorosomucoid, and its receptor, we have isolated endocytic vesicles that bind directly to and interact with stabilized endogenous hepatocyte microtubules at specific times during a synchronous, experimentally initiated, single wave of RME. Both ligand- and receptor-containing vesicles copelleted with microtubules in the absence of ATP but did not pellet under similar conditions when microtubules were not polymerized. When 5 mM ATP was added to preparations of microtubule-bound vesicles, ligand-containing vesicles were released into the supernatant, while receptor-containing vesicles remained immobilized on the microtubules. Release of ligand-containing vesicles from microtubules was prevented by monensin treatment during the endocytic wave. Several proteins, including the microtubule motor protein cytoplasmic dynein, were present in these preparations and were released from microtubule pellets by ATP addition concomitantly with ligand. These results suggest that receptor domains within the endosome can be immobilized by attachment to microtubules so that, following monensin-sensitive dissociation of ligand from receptor, ligand-containing vesicles can be pulled along microtubules away from the receptor domains by a motor molecule, such as cytoplasmic dynein, thereby delineating sorting.

=> d his

(FILE 'HOME' ENTERED AT 12:20:58 ON 28 JAN 2003)

FILE 'MEDLINE, CANCERLIT, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 12:21:06 ON 28 JAN 2003

L1 39687 S (TAXOID OR ?TAXEL OR TAXOTERE)
L2 44114 S (OROSOMUCOID OR AGP OR AAG OR ALPHA1?)
L3 53 S L1 AND L2
L4 20 S L3 AND PY<=1998
L5 11 DUP REM L4 (9 DUPLICATES REMOVED)
L6 19061 S (OROSOMUCOID OR AGP OR AAG OR ALPHA-1-ACID)
L7 54407 S TAXOID OR TAXOL OR ?TAXEL OR TAXOTERE
L8 70 S L6 AND L7
L9 27 S L8 AND PY<=1998
L10 11 DUP REM L9 (16 DUPLICATES REMOVED)